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THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

E. EDWARD KAVANAUGH
PRESIDENT

RE: Comments on Draft Guidance for Industry Photosafety Testing, Docket Number 99D-5435

The Cosmetic, Toiletry, and Fragrance Association[1] (CTFA) appreciates the opportunity to provide comments on the above referenced draft guidance document. While the guidance document does not apply to cosmetic products, the document is nonetheless of significant interest to CTFA members whose products are applied primarily by the dermal route.

The major focus of these comments is on the question of whether conducting the tests described in the testing guidance will provide information that will be useful for the assessment of human risk. Where such information is not useful for this purpose, the use of scarce resources and laboratory animals to produce data having no predictive value is questioned. In particular, CTFA does not agree that photo co-carcinogenesis testing using the mouse Skh1-*hr* albino hairless mouse for drug products which are not photoactivated will yield information useful for human risk assessment.

Additional comments/recommendations for changes to the draft guidance regarding test methods and testing considerations are also included.

- The risk of skin carcinogenesis from exposure to non-photoactivated drugs acting via alternative mechanisms is a theoretical risk. The inability of currently available methods to predict the risk to humans needs to be taken into account in the testing guidance.

  The draft guidance document cites 8-methoxypsoralen (8-MOP) as an example of a photosensitizer which tests positive in the mouse Skh1-*hr* mouse model for photo co-carcinogenesis and has been shown to increase human skin carcinogenesis risk. The mouse data for 8-MOP can thus be seen as useful for assessing human risk (i.e., identification of a photo-cocarcinogenic agent). While clear evidence of the relevance of the mouse model to human risk is limited to this one chemical, the 8-MOP example provides some basis for using the animal model to identify a human risk factor.

  In contrast, the evaluation of indirect or secondary mechanisms is quite uncertain with respect to the outcome of studies conducted in albino hairless mice. Despite this fact, the guidance document extensively discusses testing considerations of compounds that may act

[1]CTFA is the U.S. national trade association representing the personal care products industry. CTFA is comprised of over 300 active members that produce the vast majority of the cosmetics distributed in the U.S. and that also produce many over-the-counter drugs designed for dermal application. The association also has over 300 associate members that provide raw ingredients and suppliers and services to the industry. Many of CTFA's members are international companies that do business in many foreign countries as well.

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via theoretical secondary mechanisms. The document states (Section IV(B)(3), p.11) that "(s)ome of the mechanisms by which nonphotosensitizing vehicles or drugs may enhance UV-induced skin carcinogenesis include, but are not limited to, immunosuppression, neoplastic promotion, inhibition of apoptosis or DNA repair, irritation, altering the protective layers of the epidermis or changing the optical properties of the skin." It is further noted in the same section that "(s)uch mechanisms are applicable to both rodent and human skin and are biologically plausible mechanisms of enhancement."

However, with the notable exception of immunosuppressants, as used to prevent organ rejection in transplant patients, the entire premise of indirect mechanisms of enhancement is without scientifically valid experimental support. Clearly, one can speculate on mechanisms that could theoretically increase risk. Inhibiting DNA repair mechanisms or altering the protective functions of the epidermis may have an effect on UV-induced skin carcinogenesis. Such theoretically constructs, however, do not provide a basis for regulatory action.

A specific example of "other compounds (believed to) enhance UV-induced skin carcinogenesis without being photoactivated" cited in the document is "drug products that thin the protective layers of the epidermis"(Section II(A), p.3). Again, there are no data, animal or human, that experimentally support this theoretical concern. In fact, the reference cited (Pathak and Fitzpatrick, 1983 in text, 1974 in references), seemingly to support this view, provides neither data nor discussion regarding enhancement of UV carcinogenesis by such an action. Of course, if the stratum corneum were removed, more UV would penetrate. As well, the barrier function of the skin would be perturbed resulting in water loss or electrolyte imbalance. Such a physiological perturbation would need to be maintained in the absence of adaptative changes and for an extended time period, i.e., several years. Again, theoretical constructs would seem to have limited value in a practical guidance document.

An example of the difficulty associated with the application of theoretical concerns to the consideration of UV-induced skin cancers is the topical application of glucocorticoids. The use of topical steroids as anti-inflammatories has been a standard treatment for dermatological conditions for several years. Because steroids suppress the immune response and produce skin atrophy (i.e., "thinning) after repeated administration, in theory such events could be risk factors for UV-induced skin cancer. However, studies conducted in albino hairless mice have found that topical application of hydrocortisone reduced UV-induced skin tumor number and onset (Bissett *et al.*, *Photodermatol Photoimmunol Photomed*, 1990, 7:153-158). Such an effect is most likely the result of its anti-inflammatory properties. It would be an oversimplification to suggest that hydrocortisone might be a therapy to prevent UV-induced carcinogenesis, just as is the use of indirect mechanisms to postulate human risk.

In summary, the risk presented by products acting via a secondary mechanism, with the exception of immunosuppressants, is theoretical and does not translate to meaningful evaluation of human risk. The inability of currently available methods to predict the risk to humans needs to be taken into account in testing guidance. The document notes, in reference to photo co-carcinogenicity testing in a mouse model, that "because of the uncertainties involved in extrapolation from such animal testing to humans, development of alternative methods providing more relevant information for assessing the long-term adverse photoeffects of drug products relevant to humans would be desirable"(Section II(C), p.5). Mouse and human skin are significantly different in such properties as thickness of the epidermal layer and amount of pigmentation. Further, it must be recognized that there are many potential response modifiers which may have equal or greater effects on sun sensitivity

than use of dermal drug products, including the moisture content of skin, and normal seasonal variation in skin properties.

- <u>There is inadequate scientific evidence to support the concern for vehicle effects on photo co-carcinogenesis. This concern, and requirements for the evaluation of reformulations, will result in unnecessary testing</u>.

  The guidance document addresses the issue of testing of reformulations (Flow Chart A2, page 20), noting that a "new formulation (having) significantly different effects on skin that could increase phototoxicity (e.g., allows much greater penetration of UV-absorbing drug substance or excipient into the skin)" would require testing for photosensitivity. It is not clear what constitutes greater penetration of UV-absorbing drug substance or excipient. Further, an important consideration related to phototoxicology testing is the exaggerated exposure conditions inherent in the preclinical and clinical protocols. For example, in the standard phototoxicity (photoirritation) clinical protocol, product is applied under patch for 24 hr. Such conditions maximize the penetration of the "active" ingredient. Thus, changes in the formula matrix should have little impact on the outcome of phototoxicology testing.

  The document notes a concern with vehicles being photosensitizers or causing an increase in photo co-carcinogenesis. However, there is a lack of peer-reviewed data on this topic, particularly as it relates to photo co-carcinogenesis. Jacobs *et al.* (1999) is cited (Section II(B), p.4) regarding the effect of emollients on the latency for UV-induced tumors to appear in mice. However, this paper provides no peer-reviewed experimental evidence to support the "optical-clarity" hypothesis. This article is, at best, a survey of unpublished observations available exclusively to the Agency, owners of the Photosafety Guidance document, and the interpretation of such findings is very much the subject of debate. The Binder *et al.*, (1997) document is cited (Section III(A), p.6) as raising concern about the effect of vehicle, noting that "(v)ehicles may cause acanthosis, hyperkeratosis, and inflammation in rodent skin." However, this work found no effect of vehicle on measures of skin response. In fact, the point of this communication was to demonstrate similarities in the dose-response to benzoyl peroxide regardless of the vehicle. As was the case with another citation (i.e., Pathak and Fitzpatrick, 1974 or 1983) there is a need to accurately represent the information contained in such communications.

  Lastly, the document would benefit from additional clarity in the discussion of Testing Considerations (Section III). For example, what is the definition of an excipient? Are sunscreens and colors and pigments exempt from testing since it is inherent for them to absorb light and they are under other governmental review? Also, how does CDER define "persistence in eye and skin" (III.B.2) with respect to topical products?

- <u>Further guidance and discussion on the acceptability of alternative test methods would be a useful addition to the document</u>

  The document refers to the use of "alternative assays that are valid and scientifically sound." However, the term "scientifically valid" is a subjective one, and a more objective assessment of models and their interpretation is needed for a guidance document. Also, there is a distinction between a "valid method" and a "validated method." Will CDER accept methods that have not been undergone formal review and validation, such as the validation process undertaken by ICCVAM or ECVAM, in their evaluation of replacements for standard clinical/animal endpoints?

- Under Section B, Photobiologic Principals, photobiology is defined as "the study of the effect of optical radiation . . ." It is suggested that Photobiology be defined as "The study of the interaction of wavelengths in selected regions of the electromagnetic radiation (EMR) spectrum (i.e., ultraviolet, visible, infrared) with living systems" to prevent misinterpretation of the term optical (of or relating to vision). Also, in the same section, a definition is needed for "intersystem crossing" (as in "(t)he nature of a compound's excited state, the extent of intersystem crossing. . . ")

- The term photodynamic should be included in the glossary.

- On page 8, Tests for Evaluation of Photosensitivity, it is noted that the 3T3-NRU assay is "being evaluated." In fact the 3T3-NRU assay has already been officially endorsed by ECVAM as a fully validated assay.

- The Binder *et al.* abstract is referenced incorrectly. The reference should cite the 36th Annual Meeting of the Society of Toxicology, not the 37th.

- Page 4, paragraph 2, misspelled words, psoralens, anthracene, and porphyrin

Thank you for your consideration of these comments.

Sincerely,

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